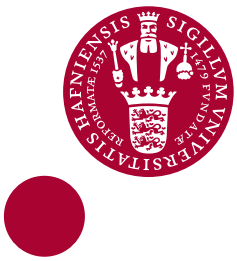

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Published in:
Dalton Transactions (Print Edition)

DOI:
10.1039/c1dt11103e

Publication date:
2011

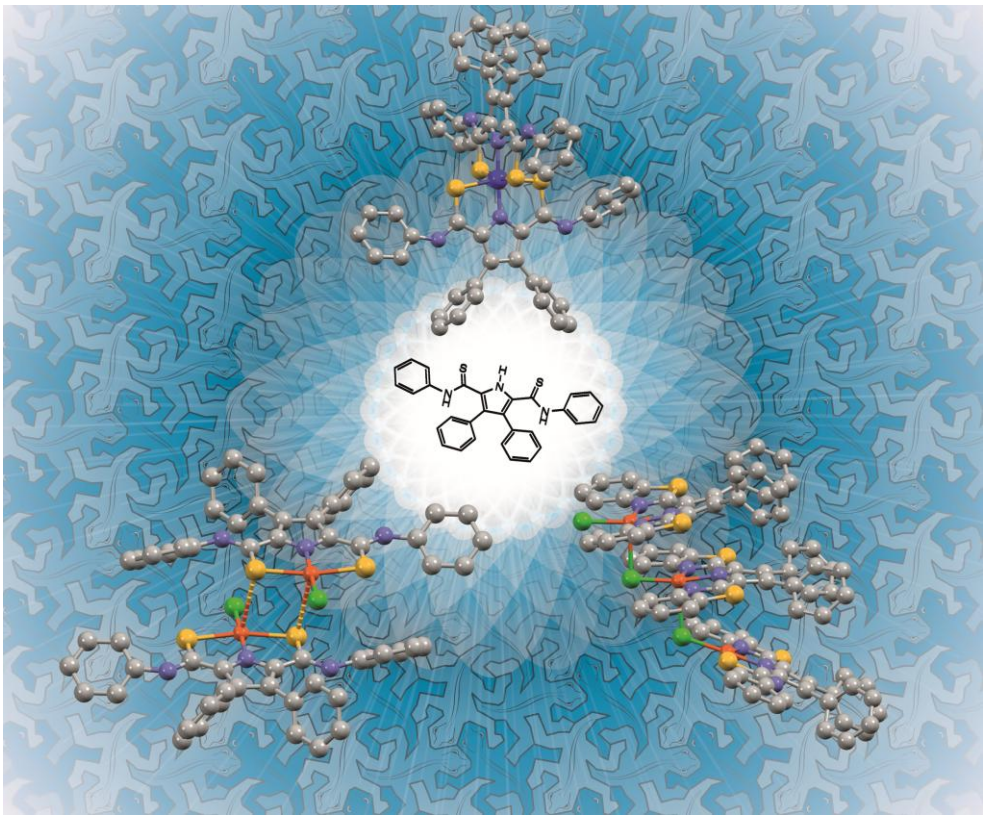
Document version
Publisher's PDF, also known as Version of record

This article is published as part of the *Dalton Transactions* themed issue entitled:

Self-Assembly in Inorganic Chemistry

Guest Editors Paul Kruger and Thorri Gunnlaugsson

Published in issue 45, 2011 of *Dalton Transactions*



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COMMUNICATION

Self-assembly between dicarboxylate ions and a binuclear europium complex: formation of stable adducts and heterometallic lanthanide complexes†

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Received 12th June 2011, Accepted 19th July 2011
DOI: 10.1039/c1dt11103e

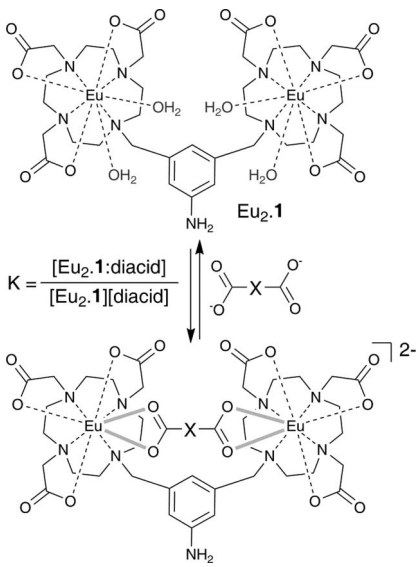
A binuclear lanthanide complex consisting of two lanthanide binding domains linked by a *m*-xylyl bridging unit forms very stable 1 : 1 adducts with benzene dicarboxylic acids and their derivatives. The complex with isophthalate derivatives is particularly stable.

The luminescence from lanthanide ions is long-lived, allowing lanthanide-centred signals to be separated from fluorescent backgrounds leading to a range of important biomedical applications, particularly in the areas of time-resolved imaging and assays.[1,2]

Since the very beginning, bioassays involving lanthanide complexes have exploited self-assembly, both in the immunological part of the assay, and in the self-assembly of brightly emissive lanthanide complexes when the assay is developed.[3] More recently, self-assembly at lanthanide centres has been applied to a wide variety of chemical systems. Self-assembled helicates containing lanthanide ions have been prepared and studied in detail,[4] and have been shown to be effective cellular imaging agents, while heptadentate lanthanide complexes have been used as responsive probes for a wide variety of anions that can coordinate to the lanthanide centre with associated displacement of water.[5] A wide variety of complex architectures can also be formed through self-assembly, including d–f hybrid complexes[6] and coordination polymers.[7]

We have previously utilised the self-assembly between carboxylates and lanthanide complexes of DO3A derivatives to establish energy transfer mechanisms in near IR luminescence,[8] and as a rapid and effective means of screening transition metal and aryl chromophores for their suitability as sensitisers of lanthanide emission.[9] We have also shown that DO3A derivatives bearing benzoate pendent arms exhibit pH dependent self-assembly that can be exploited in switching their luminescence on and off.[10]

We now report the results of a study on the self-assembly of ternary complexes between the binuclear lanthanide complex Eu_2·**1** and a series of dicarboxylate ions, and illustrate how such an approach can be used to assemble heterometallic lanthanide complexes. We recently reported the synthesis of **1** and its lanthanide complexes,[11] which we have found to offer a high degree of kinetic stability, to the point where they are stable even in the conditions required for diazotisation and incorporation into azo dyes.[12] This system also contains two lanthanide centres in close proximity, which can potentially bind to two anionic donors to form a chelating ligand, as shown in Scheme 1.



Scheme 1 Binding of diacids by binuclear lanthanide complex Eu_2·**1**.

We initially investigated the self-assembly of heterometallic systems by direct extension of our work on pH responsive probes based on lanthanide complexes of **2**. We attempted to favour heterometallic self-assembly on electrostatic grounds by binding of

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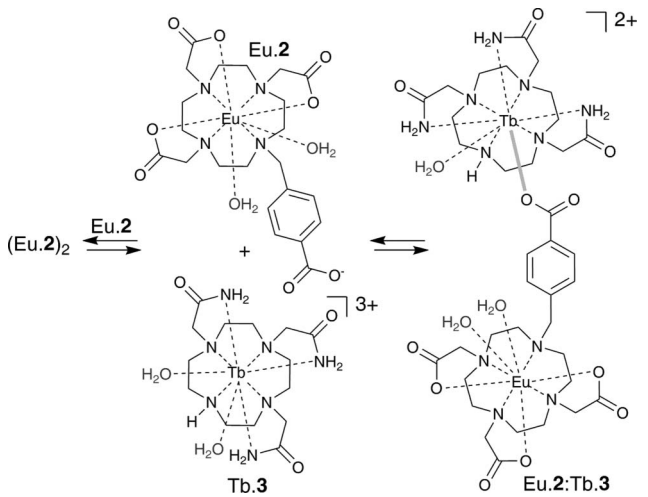
† Electronic supplementary information (ESI) available: Titration and fitting methodology, DynaFit script example and binding studies of acids with a mono- and a bi-metallic lanthanide complex are available as supporting information. See DOI: 10.1039/c1dt11103e

2 to [Tb·**3**]$^{3+}$ as shown in Scheme 2. In such a system, excitation of the benozate chromophore should only sensitise terbium emission effectively when the bimetallic complex is assembled. Data from a titration of Eu·**2** with Tb·**3** are shown in Fig. 1. These data cannot be interpreted with a simple binding model. Both complexes are heptadentate and the binding occurs without discrimination as indicated in Scheme 2. The speciation is complicated further by the possibility of both mono- and bi-dentate binding of the carboxylic acid to the lanthanide centre. Thus, a minimum of five species has to be taken into account in the data analysis. From the data presented in Fig. 1 it was not possible to determine which species, if any, dominates. It follows that no binding constants could be determined. However, it is clear from the switching on of the terbium centred luminescence that self-assembly is occurring. It is known that the binding of benzoic acids to lanthanide centres have binding constants in the order of $K \approx 10^4$ M^{-1}.[13] For most practical applications this value is too low, as the self-assembled



Scheme 2 In Eu_2·**2** and Eu_2·**2** : Tb·**3** the binding of the carboxylate to the lanthanide (shown bold in grey) can be either mono- or bi-dentate.

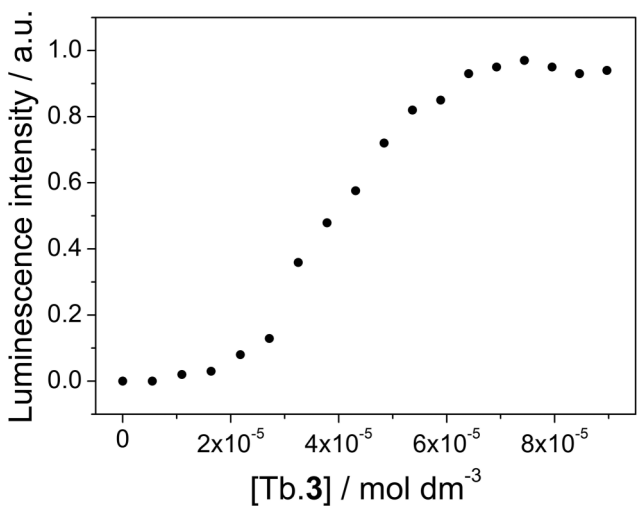


Fig. 1 Titration of a 10^{-5} M solution of Eu_1·**2** with 5 µl aliquots of a 22 mM solution of Tb·**3** in water monitored at 545 nm with 240 nm excitation.

Table 1 Binding constants of Eu_2·**1** : diacid complexes in 3 : 1 methanol–water determined using either the intensity or the lifetime of the europium emission. See ESI for details.† The 99% confidence intervals are given in brackets where they could be determined

Complex	*K* Intensity [M^{-1}]	*K* lifetime [M^{-1}]
Eu_2·**1** : **4**	12 110 [9 107–15 230]	—
Eu_2·**1** : **5**	—	30 000
Eu_2·**1** : **6**	$>20 \times 10^6$	$>2 \times 10^6$
Eu_2·**1** : **7**	1.9×10^6 [1.3×10^6–3.0×10^6]	$>2 \times 10^6$

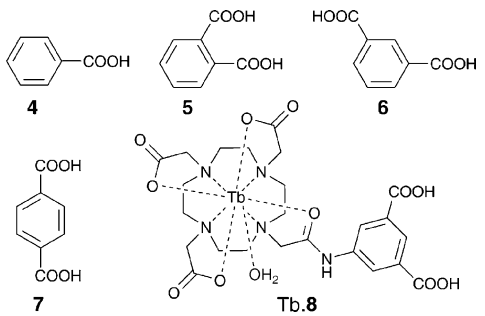
Table 2 Binding constants determined using emission intensity

Complex	Solvent	*K* [M^{-1}]	99% confidence interval	Emitter
Eu_2·**1** : Tb·**8**	PBS	225 600	216 370–235 420	Tb·**8**
Eu_2·**1** : Tb·**8**	HEPES	226 500	208 550–246 920	Tb·**8**

structure will be disassembled by phosphate in aqueous media or serum.

We next chose to study the binuclear system Eu_2·**1** and its binding of phthalic acids. In this system, two carboxylate groups can bind to a metal centre and the electron deficient aromatic ring of the phthalate may dock with the electron rich aniline ring linking the two metal ligands. While Eu_2·**1** is charge neutral, some residual positive charge will reside on the lanthanide centres, meaning that electrostatic effects can still play a role in modulating self-assembly.

We performed a series of binding studies of Eu_2·**1** and benzoic acid (**4**), phthalic acid (**5**), isophthalic acid (**6**) and terephthalic acid (**7**) to determine the degree of selectivity that could be achieved through self-assembly. Due to low solubility the studies were performed in a mixture of methanol–water. The structures of the acids used are shown in Scheme 3 and the binding constants are tabulated in Table 1. Experimental details and data are given as electronic supporting information.†



Scheme 3 Acids used in the self-assembly of structures based on Eu_2·**1**.

The data was fitted to several binding models using DynaFit.[14] The binding constants were determined and the best possible binding model was found aided by the software.[15] The binding constants were determined independently from lifetime and intensity data.

The binding equilibrium is shown in Scheme 1. Whether each carboxylates act as monodentate or bidentate donors is open

to question, though previous reports indicate that each metal centre in Eu_2·**1** is bound to one water molecule.[11] Binding of an acid can occur with liberation of the water or by going from an eight-coordinate complex to a coordination number of nine.

The gain of the binding in the bidentate of the complex is evident as $K(Eu_2·\mathbf{1}:\mathbf{4}) = 12\,000\ M^{-1}$ and $K(Eu_2·\mathbf{1}:\mathbf{7}) = 1.9 \times 10^6\ M^{-1}$. The binding of benzoic acid to Eu_2·**1** is 1000 fold weaker than the bidentate binding. This increase alone removes the concern of the competitive binding of phosphate. There is considerable debate in the literature as to the nature of chelate cooperative binding,[16] and both cooperative and non-cooperative mechanisms could play a part in binding, but these do not concern us for the purposes of this preliminary communication.

All benzene diacids or phthalates can potentially partake in bidentate binding to Eu_2·**1**. Phthalic acid can for steric reasons not bridge the complex and the binding is low $K(Eu_2·\mathbf{1}:\mathbf{5}) = 30\,000\ M^{-1}$. Iso- and terephthalic acid can bridge the binding pocket and bind to both metal centres. The question is which acid is best matched to the binding pocket. Inspection of Table 1 gives the answer, as isophthalic acid binds at least 10 times more strongly than the terephthalic acid. In this solvent system isophthalic acid binds to Eu_2·**1** with a binding constant larger than we are capable of measuring. Thus the optimal system for self-assembly is a combination of Eu_2·**1** and an isophthalic acid derivative.

We then turned our attention to using isophthalate appended lanthanide complexes in the self-assembly of a heterometallic array. To obviate the problem of self-association experienced with Eu·**2**, we elected to use Tb·**8**,[17] which makes use of an octadentate ligand in this phase of the study. Tb·**8** was self-assembled with Eu_2·**1** in two different aqueous buffer systems, namely a competitive phosphate (PBS) and non-competitive ammonium–sulfonate buffer (HEPES). Both buffers were adjusted to pH = 7.4, where the isophthalate is fully deprotonated. The self-assembly was followed by emission spectroscopy. The titrations were performed as described above and in the ESI,† but in this case only the terbium emission could be monitored owing to the intense terbium centred emission from the Eu_2·**1**:Tb·**8** complex. A typical dataset is shown in Fig. 2. The binding constants were determined from several different datasets and are reported in Table 1. The binding of the isophthalate motif of Tb·**8** in aqueous buffer is a factor of 100 weaker than in the mixed solvent system, but still so strong that there is no difference between the buffers.

Conclusions

In this paper, we have shown how heterometallic lanthanide complexes can be prepared by spatial matching of the interactions between two kinetically stable complexes. Furthermore, bidentate donors such as isophthalate can be exploited to give tightly bound systems that remain assembled even in the presence of competitor ions such as phosphate. This raises a number of exciting possibilities, notably that it may be possible to self-assemble much more complicated lanthanide architectures from well-designed building blocks. We are currently investigating the prospects for such systems.

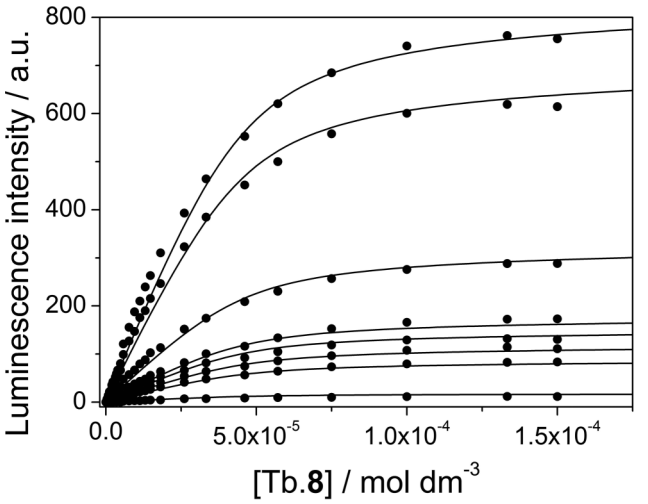


Fig. 2 Titration of a 2×10^{-5} M solution of Eu_2·**1** with Tb·**8** in PBS solution. The traces are recorded at several wavelengths with 240 nm, 397 nm and 488 nm excitation.

Acknowledgements

The authors thank the University of Oxford for support, and the Danish Council for Independent Research, Technology and Production Sciences (grant 10-093546) for financial support for TJS.

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